Health Canada's Proposal to Accelerate New Drug Reviews

Proposition de Santé Canada pour accélérer la politique d'examen des nouveaux médicaments

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Abstract

Health Canada is proposing to update its accelerated review pathways to get important new drugs into the market more quickly. To date, the two pathways that Health Canada uses have not demonstrated that they can identify therapeutically valuable new drugs. Drugs approved under the two pathways also have a greater likelihood of acquiring a serious safety warning post-marketing compared with drugs approved through the standard review pathway. The new proposals from Health Canada will not go far in rectifying this situation, and major changes are needed. Health Canada needs to present evidence that the changes it is proposing will actually allow these pathways to fulfill the set objectives and support health benefits for Canadians.

Résumé

Santé Canada propose une mise à jour de ses processus d'examen accéléré pour mettre plus rapidement sur le marché de nouveaux médicaments importants. À ce jour, il n'est pas démontré que les deux processus employés par Santé Canada permettent d'identifier de nouveaux médicaments qui soient profitables sur le point thérapeutique. Les médicaments

approuvés en vertu de ces deux processus sont aussi plus susceptibles de donner lieu à des avertissements sérieux après leur mise en marché, comparativement aux médicaments approuvés selon les processus d'examen normaux. La proposition de Santé Canada ne permettra pas de rectifier cette situation et d'importants changements sont nécessaires. Santé Canada doit présenter des preuves que les changements proposés permettront effectivement à ces processus d'atteindre les objectifs établis et d'apporter des avantages en matière de santé pour les Canadiens.

Introduction

To obtain authorization to market a new active substance (NAS, a molecule never marketed before in Canada in any form), companies typically file a new drug submission (NDS) with Health Canada, which includes preclinical and clinical scientific information about the product's safety, efficacy and quality and information about its claimed therapeutic value, conditions for use and side effects (Health Products and Food Branch 2006). Health Canada then has a 300-day period to evaluate this information and make a decision about whether to allow the product to be sold, that is, whether to issue a notice of compliance (NOC).

In an effort to ensure that promising therapies for serious, life-threatening or debilitating illnesses reach Canadians in a timely manner, Health Canada has developed two other pathways for approving an NAS. These are described in detail elsewhere (Lexchin 2015b), but, briefly, the first of these is a priority review that involves the company submitting a complete NDS but with a review period of 180 days (Health Canada: Health Products and Food Branch 2009). The second is the NOC with conditions (NOC/c; Health Canada 2016), whereby Health Canada will give a conditional approval based on limited evidence – Phase II clinical trials or trials with only surrogate markers. In return for NOC/c status, companies commit to further studies that definitively establish efficacy and submit the results of these to Health Canada. If these studies are not completed or negative results are obtained, it could lead to the cancellation of marketing authorization. Collectively, these two review pathways are referred to, in this article, as accelerated reviews.

Health Canada began a regulatory review of drugs and devices in 2017, and as part of this process, it issued a "Draft Guidance: Accelerated Review of Human Drug Submissions" to update its accelerated review pathways (Health Canada 2019) and conducted a consultation on that document from May 7 to July 21, 2019 (Government of Canada 2019). In the document, Health Canada lays out three policy objectives:

> support earlier access by way of shortened review times, to new or promising new drugs ... better align Health Canada's prioritization of drug reviews with the needs of the Canadian health system; and ensure transparency of any conditions that may be associated with a market authorization.

I argue that a review of Health Canada's two accelerated review programs is necessary, and in this analysis article, I will present evidence that has been published in a series of research articles starting in 2012, which shows that neither of these programs is achieving their objectives. I then compare Health Canada's record in using accelerated reviews with other regulatory authorities' record of the same. Finally, I critique the proposals from Health Canada and offer suggestions for more fundamental reforms.

Much of the analysis that I will be presenting is based on evaluations of the additional therapeutic effectiveness of new drugs. Those evaluations are drawn from two sources – *Prescrire*, the English language version of the French drug bulletin *Prescrire International* and the ratings produced for the Canadian Patented Medicine Prices Review Board (PMPRB) by its Human Drug Advisory Panel (HDAP). Both organizations use rigorous methodology and produce unambiguous evaluations of therapeutic value. In deciding on the level of therapeutic innovation, HDAP considers two primary factors – increased efficacy and reduction in the incidence or the grade of important adverse reactions – and nine secondary factors – route of administration, patient convenience, compliance improvements leading to improved therapeutic efficacy, caregiver convenience, time required to achieve the optimal therapeutic effect, duration of usual treatment course, success rate, percentage of affected population treated effectively and disability avoidance/savings. The primary factors are given the greatest weight, followed by an assessment of any additional improvement as a result of the secondary factors (PMPRB 2014). *Prescrire* assesses the therapeutic value of medicines through a multistep process. First, it "examines the condition or clinical setting for which the drug is proposed; then the natural course of the disease, the efficacy and safety of existing treatments, and the most relevant outcome measures. This is followed by a systematic search for clinical data on the efficacy and adverse effects of the new drug, and an assessment of the level of evidence. Based on [its] independent analysis of clinical data, [it] form[s] a judgement as to whether or not the new drug is beneficial for patients or whether or not its harmful effects outweigh the benefit" (Prescrire Editorial Staff 2011).

Evaluation of Health Canada's Current Accelerated Review Pathways

Priority review

A total of 426 drugs were approved by Health Canada between 1997 and 2012. Of these, 345 were evaluated by the PMPRB and/or the French drug bulletin *Prescrire International* (English version) to determine if they offered a significant therapeutic improvement over the drugs already on the market. Only 52 of the 345 (15.1%) were rated as innovative, but Health Canada gave a priority review to 91 of these (26.4%).

The therapeutic value of new drugs as determined by the PMPRB and/or *Prescrire International* was compared with whether the drugs received either a priority or standard review from Health Canada using kappa values that measure interrater agreement – in this case whether Health Canada's decision to use a priority review for individual new drugs

aligned with their therapeutic value. Yearly kappa values comparing the therapeutic evaluations given by Health Canada and by the PMRPB and/or *Prescrire International* on an individual drug level ranged from a low of −0.091 in 1998 to a high of 1.000 in 2010. Kappa values were at or below 0.400 in nine of the 16 years, meaning a level of agreement of fair or less in those years. The overall kappa for the 16 years was 0.334 or fair. There is no evidence that Health Canada's ability to determine which products offer significant therapeutic gain improved over the time that Health Canada has been granting priority approvals.

Based on a drug-by-drug comparison for all drugs evaluated by the PMPRB and/or *Prescrire International*, the positive predictive value of Health Canada's ratings was 36.3%, meaning that it gave a priority review to 91 drugs, but only 33 were evaluated as innovative (Lexchin 2015a).

An analysis comparing post-market safety of drugs approved through the priority and standard review pathways found that, if the products received a standard review, there was a 19.8% chance that Health Canada would issue a serious safety warning about the drug compared with a 34.2% chance for a drug with a priority review. The possibility that these differences could be explained by either the mechanism of action of the drug in question or by the seriousness of the diseases that priority review drugs were indicated for were both investigated and rejected (Lexchin 2012).

Finally, Health Canada gives a priority review to over 40% of first-in-class drugs, but only 16% have significant therapeutic advantages over existing products (Lexchin 2016).

Notice of Compliance with conditions

From the inception of the NOC/c policy in 1998 to the end of 2017, there were 89 NOC/cs issued for 70 unique drugs – 52 for new drugs and 37 for new indications for existing drugs. New drugs approved with an NOC/c represented 9.5% of 546 new products approved by Health Canada. The PMPRB and/or *Prescrire International* evaluated the additional therapeutic value of 78 of the new drugs or new indications for existing drugs, and 54 (69.2%) offered minimal to no additional therapeutic value. As with the priority approval pathway, there is no evidence of any improvement in Health Canada's ability to determine whether products approved under this policy offer significant therapeutic gains.

A total of 50 NOC/cs (56.2%) were fulfilled and 31 (34.8%) were not fulfilled, and in eight (9.0%) cases, either the indication or the drug was withdrawn. The median time to fulfillment was 1,040 days. Twelve NOC/cs took more than five years to fulfill their conditions. The unfulfilled NOC/cs had been issued for a median of 1,161 days, and 10 had been outstanding for more than five years (Lexchin 2018b).

Comparing post-market safety of drugs approved through the NOC/c policy with that of drugs approved through a standard review shows that the former was more likely to acquire a serious safety warning than the latter (Lexchin 2015b).

Many of the confirmatory studies that Health Canada accepted as fulfilling the conditions had significant limitations. Twenty (55.6%) of the 36 studies used surrogate outcomes,

the median age of patients in all of the studies was under 60 years and except for four (14%) out of 29 studies, men outnumbered women (Lexchin 2018c).

Finally, Health Canada is lacking transparency, given that it does not provide any public information about the status of confirmatory studies that have not been completed.

Both accelerated review programs combined

From January 1, 1995, to December 31, 2016, Health Canada approved a total of 623 NASs. Out of these, 509 (81.7%) were evaluated for their therapeutic innovation either by the PMPRB and/or *Prescrire International*. Health Canada used an accelerated review pathway for 159 of the 509 drugs, whereas only 55 were judged to be therapeutically innovative by one or both of the independent reviews. Forty-two of the 55 drugs that were therapeutic innovations received an accelerated review, 13 received a standard review and 117 that were not therapeutic innovations also received an accelerated review. There was poor concordance between Health Canada's decision that a drug merited an accelerated review and assessments of the drug's therapeutic value. The kappa value comparing the therapeutic rating from PMPRB and/or *Prescrire International* to the use of Health Canada's accelerated review programs for the entire period for all 509 drugs was 0.276, a value considered as "fair agreement" (Lexchin 2018a).

Quality of Reviews: Health Canada vs. Other Regulatory Authorities

Research in other jurisdictions has also evaluated the post-market safety and degree of therapeutic innovation of drugs approved through accelerated pathways. The evidence about whether accelerated reviews lead to more post-market safety issues is mixed. One American study (Mostaghim et al. 2017) found an association between shorter review times and more safety warnings. But faster regulatory review speed by the European Medicines Agency (EMA) was not associated with a greater likelihood of post-market safety events (Zeitoun et al. 2015), and a second US study found that post-market events were statistically significantly less frequent among drugs with shorter review times (Downing et al. 2017). The evidence about how well regulatory agencies can predict which drugs approved through accelerated reviews will offer significant therapeutic advances is more uniform, at least with regard to oncology drugs. After a median follow-up of 4.4 years, only one of 15 oncology drugs approved by the Food and Drug Administration (FDA) through an accelerated pathway had a definite survival benefit, compared with six in which there was no survival benefit and eight in which the overall survival benefit was unknown (Kim and Prasad 2015). A second study of 93 oncology drugs granted an accelerated approval by the FDA between December 1992 through May 2017 found that confirmatory trials demonstrated improvements in overall patient survival for only 19 products (Gyawali et al. 2019).

Health Canada's Proposals for Accelerated Approvals

What I present here is not a comprehensive examination of the proposals in Health Canada's draft guidance document, but rather it is meant to show the weaknesses in some of the measures that Health Canada plans to introduce. To qualify for an accelerated approval, Health Canada states that

> the sponsor should be able to demonstrate that the therapy provides – or has the potential to provide – a statistically significant and clinically relevant improvement in efficacy or decrease in risk such that the overall benefit/risk profile is improved over any available therapy or drug marketed in Canada.

However, relying on the sponsor, who stands to financially benefit from getting the drug to market faster, to be objective about its product is not sufficient. Before making a decision about using an accelerated pathway, Health Canada should convene a panel of independent clinical experts to seek their advice about the likelihood that the product under consideration would be a significant therapeutic advantage and be at least as safe as existing therapies for the same condition.

The draft guidance encourages sponsors to request a pre-submission meeting with Health Canada, i.e., a meeting that would take place before filing the documentation for approval, so that the sponsor can outline the evidence of effectiveness for Health Canada. The EMA conducts similar meetings and the European Ombudsman organized public consultations on this practice. In response, the International Society of Drug Bulletins and *Prescrire* filed a presentation pointing out that by providing advice, the "EMA puts itself in a position where it assists companies…by telling them the level of clinical evaluation it is likely to consider adequate to issue a positive opinion on a marketing authorisation application," thus creating a conflict-of-interest (COI) situation (International Society of Drug Bulletins and Prescrire 2019). The presentation forcefully made the point that the EMA should have a procedure for managing these COIs that includes "measures that enable the public to freely and easily verify that nobody who provided pre-submission scientific advice on a medicine is involved in assessing any subsequent marketing authorization applications for the same medicine." The draft guidance from Health Canada neither makes any mention of having a distinction between the Health Canada officials who attend the pre-submission meeting and those who eventually will be evaluating the documentation nor does it deal with public access to information about who from Health Canada attended the meeting.

Notably absent from the draft guidance are any specific requirements for the evidence that companies will have to present to get their drugs approved through an accelerated pathway. Previous research has shown that drugs approved based on trials that used surrogate outcomes, used placebo controls and enrolled small numbers of patients and were short-term are more likely to overestimate or generate spurious treatment effects (Davis et al. 2016).

The only reference to evidentiary requirements in the draft guidance is the following statement:

> When received, it is expected that the submission will contain the information and material for the purposes of Division 8, Part C of the *Food and Drug Regulations* and be subject to the *Guidance Document: Management of Drug Submissions and Applications*.

Health Canada should be demanding higher premarket evidentiary standards when considering drugs for an accelerated review, or if the evidence is not available in the premarket period, it should make approval conditional on that evidence being generated in the post-market phase. Specifically, unless there are strong reasons for not doing so, clinical trials should have to use hard clinical outcomes instead of surrogate outcomes, comparators should be existing therapies rather than placebo controls, trial times should be long enough to detect rarer safety issues and validate ongoing treatment benefits, and except for drugs for orphan diseases, patient numbers should be large enough to look at important subgroups.

Finally, for drugs approved through the NOC/c pathway, the draft guidance goes into considerable detail about the requirements that companies have to meet in the post-market phase, including providing yearly status reports on the progress of ongoing confirmatory trials. However, there is no mention that either a full description of the trials or the status reports about them must be publicly available.

Conclusion

This review has shown that there is a lack of clear evidence of therapeutic benefits for most drugs approved through these two pathways and of a higher rate of serious post-market safety concerns for drugs that have been approved more rapidly as compared with standard review process. Specifically, the following serious deficiencies exist in the two accelerated review programs:

1. The large majority of drugs approved under both the priority review program and the NOC/c pathway do not offer any significant therapeutic improvement over drugs already on the market.
2. Drugs approved through either pathway are more likely to acquire a serious safety warning compared to drugs approved through the standard review pathway.
3. Health Canada's ability to determine which products approved under the two accelerated review pathways offer a significant therapeutic gain has not improved over the time that these pathways have been in operation.
4. The confirmatory studies that Canada accepts to remove conditions for drugs approved under the NOC/c policy have significant limitations.

5. Health Canada lacks transparency about the confirmatory studies that need to be completed for drugs approved under its NOC/c policy. Specifically, it provides no publicly available information about confirmatory studies that have not been completed and studies for some drugs have not been completed for over five years.

The rationale for using accelerated review pathways is to get important therapeutic advances to patients in a timely manner, but Health Canada's use of these pathways to date has not fulfilled this objective, and its proposals in the draft guidance will not correct this situation. Moreover, the use of these pathways comes with both health-related costs and resource costs. Before any changes are made, Health Canada needs to present evidence that the changes it is proposing will actually allow these pathways to fulfill the objectives that it has set out for them and lead to significant health benefits for Canadians.

Competing Interests

From 2016 to 2019, Joel Lexchin was a paid consultant on two projects: one looking at developing principles for conservative diagnosis (Gordon and Betty Moore Foundation) and the other deciding what drugs should be provided free of charge by general practitioners (Government of Canada, Ontario Supporting Patient Oriented Research Support Unit and the St Michael's Hospital Foundation). He also received payment for being on a panel at the American Diabetes Association, for giving a talk at the Toronto Reference Library, for writing a brief in an action for side effects of a drug for Michael F. Smith, Lawyer and, from the Canadian Institutes of Health Research, for presenting at a workshop on conflict-of-interest in clinical practice guidelines. He is currently a member of research groups that are receiving money from the Canadian Institutes of Health Research and the Australian National Health and Medical Research Council. He is a member of the Foundation Board of Health Action International and the Board of Canadian Doctors for Medicare. He receives royalties from University of Toronto Press and James Lorimer & Co. Ltd. for books he has written. There was no funding associated with this study.

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